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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,056	01/02/2004	Gerianne Tringali DiPiano	FEM 104	1945

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EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,056	DIPIANO ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/1/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,8,10-12,14,15,17 and 19* is/are pending in the application.

4a) Of the above claim(s) *10-12, 14, 15, 17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 1, 2009 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 5 7, 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ragavan (WO 00/72883A2, Ragavan-WO).

Ragavan-WO claimed a topical formulation comprising a penetration enhancer, the penetration enhancer consisting essentially of a diol and a cell envelope disrupting agent where in the cell envelope disordering agent is **oleic acid** and/or **oleyl alcohol** and **danazol** as a pharmaceutically active agent. Ragavan-WO claimed that the

formulation is useful for **transdermal** administration. (claim 11). Ragavan teaches that the transdermal permeation is primarily controlled by diffusion through the **stratum corneum**. (page 1, lines 5-23). Ragavan teaches that the carriers such as **water**, oil, lotions, **hydrogels** and solvents such as **ethanol and isopropanol** can be employed. (page 5, lines 22-34). Applicants' recitation in claims 1 of an intended use to relief from disease or disorders of the breast do not represent a patentable limitation since such fails to impart any physical limitation to the composition since the prior teaches same formulation comprising the same active agent claimed by Applicants.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ragavan (WO 00/72883A2) (Ragavan-WO) as applied to claims 1-2, 4, 5 7, 8 and further in view of Ragavan et al. (U.S.Patent No. 5,993,856) (Ragavan1) of record.

Ragavan-WO as applied as before.

Ragavan-WO does not teach micro- or non-particles of danazol.

Ragavan-1 teaches that topical formulation of danazol can be formulated as micro or a nanoparticle is known in hydrogel formulations. (abstract). Ragavan-1 teaches the micronized danazol can be manufactured by Cipla Pharmaceuticals can be bought from Byron Chemical company. (Example 1). Ragavan-1 also teaches that

danazol in a micro or nanoparticulate formulation can be achieved by milling of the drug or atomization of drug solution, for example, into a solvent extraction fluid, or other standard techniques. (column 3, lines 10-15).

It would have been obvious to one of ordinary skill in the art to modify danazol formulation of Ragavan-WO and formulate danazol as micro or nanoparticles because micro particle formulation can be either obtained by milling of drug (danazole) or can be bought from Byron Chemical company. Further, Ragavan-1 teaches that danazol in micro or nanoparticles are routinely employed in a gel formulation as exemplified in his example 1. One would have been motivated to employ danazol in either micro or nanoparticles formulation well known in the art as readily available and can be routinely manufactured by standard techniques (e.g. milling) as taught by Ragavan-1.

Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ragavan et al. (U.S.Patent No. 5,993,856, Ravagan1) of record.

Ragavan et al. teach a micro or nanoparticulate drug formulation for topical administration comprising danazole or anticancer drug, anti-proliferative drug in an effective amount formulated in foams, gel, lotion, suspension, solution, ointment and cream. (abstract, claims particularly, claims 31-33, Examples 1-3, column 3, lines 10-21). Ragavan et al., at column 9, Example 3, where it teaches that microparticle danazol is formulated with the presence of poly(vinylpyrrilodine) (also known as PVP). Ragavan et al. teach that the formulation can be formulated as the micro or nano particulates. (see claims 6 and 7). Ragavan et al. illustrate the gel composition. as well as the employment of alcohols as an excipients, and hydrogel microspheres made

of gel-type polymers for the composition. (Example 1, column 3, lines 15-37, column 4, line 10, column 6, lines 43-45). Ragavan et al. teach that sorbitan esters and triethanolamine (penetration enhancers) can be employed in the formulation. (column 4, lines 4-16). One of ordinary skill in the art would readily recognize that poly(vinylpyrrilodine) is a penetration enhancer. Ragavan et al. teaches that the microparticle danazol comprises 10mg/day, 25mg/day, 50mg/day. (Example 3). These dosages are within and/or overlap Applicant's preferred danazol dosage rage in the specification on page 9, under dosage. Ragavan et al. illustrate 1mg gel formulation comprising microparticulate formulation of danazol in Examples 1 and 2. Ragavan et al. illustrate that danazole concentrations of 1mg/300g rat were administered and danazol concentrations of 100mg /50kg were administered to women. (table 1). These dosages are within Applicant's dosage range of danazol in the specification page 9. Ragavan et al. teach that the formulation provides significantly diminished side effects with increased bioavailability and comfort. (column 3, lines 15-20). Ragavan et al. teach that the formulation provide less amount of danazol in systemically compared to topical. (see claim 1). Ragavan et al. on column 6, lines 43-50, column 8, example 2, teaches that the hydrogel microspheres that are employed as carriers are made of gel-type polymers that were prepared by dissolving the polymers in an **aqueous** solution.

Ragavan et al. do not illustrate the danazole formulation formulated with a hydroalcoholic gel carrier, the formulation providing relief from disease or disorders of the breast and the property of the carrier capable of delivering the drug to the breast

tissue and to promote delivery of the drug across the stratum corneum with low serum drug levels compared to the systemic administration of the drug.

It would have been obvious to one of ordinary skill in the art to modify the Ragavan et al.'s illustrated danazol and PVP formulation by employment of hydroalcoholic gel because Ragan et al. teach that the danazol formulation can be formulated as a gel with the employment of hydrogel microspheres of gel-type polymers together with alcohols as a excipients or carriers as taught by Ragavan et al. One of ordinary skill in the art would have been motivated to make such a modification in order to achieve an expected various topical danazol formulation including gel formulation taught by Ragavan et al. with a reasonable expectation of providing significantly diminished side effects with increased availability and comfort topically as taught by Ragan et al. Applicants' recitation in claims 1 of an intended use of treating benign diseases of the breast and to relief from disease or disorders of the breast do not represent a patentable limitation since such fails to impart any physical limitation to the composition since the prior teaches same formulation comprising the same active agent with the same "effective amount" as claimed by Applicants. Further, the limitation of the carrier "capable" of delivering the drug for the breast tissue, it is noted that the carriers or excipients employed by Ragan et al. is the same "penetration enhancer" as required by claim 1. Therefore, the same compounds cannot have mutually exclusive properties. Accordingly, the same penetration enhancer taught by Ragan et al. would be "capable" of delivering the drug for the breast tissue and promote delivery of the drug across the stratum corneum upon the contact with skin during an administration step.

Applicants' recitation of the intension of delivering the drug across the stratum corneum must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended delivery, then it meets the claim. In this case, Ragavan 1 teaches the same active agent (danazol), the same penetration enhancer (e.g. PVP) and the same amount effective (50mg/day danazol, see Example 3 of Ragavan) that is the amount effective to provide regional, not systemic, relief from benign dieses or disorder disclosed in the instant specification. (see the specification page 9, under dosage). Therefore, Ragavan1 formulation would have the same functional characteristics such as promoting delivery of the drug across the stratum corneum. Moreover, Ragavan in their claim 1 teach that the formulation provide the amount less than the amount when the drug is administered systemically. Accordingly, the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7 and 8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 31-33 of U.S. Patent No. 5,993,856 (Ragavan1). Although the conflicting claims are not identical, they are not patentably distinct from each other because it encompasses same subject matter. The claims in patent teach a micro or nanoparticulate drug formulation for topical administration comprising danazole or anticancer drug, anti-proliferative drug in an effective amount formulated in foams, tablets and creams and same “effective amounts” of treating a diseases or disorder in a regions overlap with instantly claimed “effective amounts” to provide relief from disease or disorders of the breast.

Claims 1-5, 7 and 8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 17 of U.S. Patent No. 6,652,874 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because it encompasses same subject matter. The claims in

patent teach a drug formulation comprising the drug selected from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs formulated in micro or nanoparticulate with same "effective amounts" of treating a diseases or disorder in a regions overlap with instantly claimed "effective amounts" to provide relief from disease or disorders of the breast. (see example 3, and instant dosage range in the specification on page 9).

Claims 1-5, 7 and 8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 12 of U.S. Patent No. 6,416,778 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because it encompasses same subject matter. The claims in patent teach a drug formulation including liquid suspension, hydrogel or topical ointment or a cream comprising the drug particles danazole for regional administration of an effective amount to provide relief from symptoms of a disease or disorder with same "effective amounts" of treating a diseases or disorder in a regions overlap with instantly claimed "effective amounts" to provide relief from disease or disorders of the breast. (see example 3, and instant dosage range in the specification on page 9).

None of the claims are allowed.

Response to Arguments

Applicants' arguments filed August 31, 2009 have been fully considered but they are not persuasive. Applicants argue that Ragavan1 does not disclose a hydroalcoholic carrier, much less that a transdermal penetration enhancer should be included in the formulation. Applicants further argues that the formulation of Ragavan 1 are intended for delivery across the mucosal membrane which does not present the difficulty associated with transport through the skin. This is not found to be persuasive because in view of Applicants' examples in the specification, it appears that Applicants' "hydroalcoholic carrier" is merely a gel formulation comprising alcohol combined with an aqueous component. Ragavan1 illustrates the gel composition as well as the employment of **alcohols** as an excipients, and hydrogel microspheres made of gel-type polymers for the composition. (Example 1, column 3, lines 15-37, column 4, line 10, column 6, lines 43-45). Applicants' attention is drawn to Ragavan1, column 6, lines 43-50, column 8, example 2, where it teaches that the hydrogel microspheres that are employed as carriers are made of gel-type polymers that were prepared by dissolving the polymers in an **aqueous** solution. On column 9, Example 3 of Ravagan-1, it teaches that microparticle danazol is formulated with the presence of poly(vinylpyrrilodine) (also known as PVP). One of ordinary skill in the art would readily recognize that poly(vinylpyrrilodine) is a penetration enhancer because it is well known in the art by D'Angelo et al. (U.S.Patent No. 5,614,212), see abstract, column 7, lines 43-46. Ragavan 1 teaches the same active agent (danazol), the same penetration enhancer (e.g. PVP), the same amount effective (50mg/day danazol, see Example 3 of

Regavan 1) with carriers such as alcohol and polymers that are prepared by dissolving in aqueous solution. It is noted that the amount effective to provide regional, not systemic, relief from benign dieses or disorder in Ravagan-1 is the same effective amount that is disclosed in the instant specification. (see the specification page 9, under dosage). Therefore, Ragavan1's formulation would have the same functional characteristics such as promoting delivery of the drug across the stratum corneum. Applicants' recitation of the intension of delivering the drug across the stratum corneum must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.

Applicants argue that the example 1 of the instant application and the declaration under C.F.R. 1.132 submitted with the amendment and response, both clearly demonstrate statistically significant unexpected results. Applicants argue that the statements 5-9, experiments were designed to test the skin permeability of an intravaginal formulation such as those disclosed in Ragavan 1 and the data presented in Exhibit 2, page 6, Table 3, indicate that this formulation was ineffective at penetrating the skin. Therefore, this experiment demonstrates that the formulation of Ragavan 1 do not penetrate the stratum corneum. The declaration has been carefully considered and reviewed. However, it is not persuasive because the declaration on page 2 states that "**a transvaginal** danazol formulation is ineffective when applied to the skin because it does not permeate the stratum corneum" (see item 5); the exhibit 1 illustrate the **"quantitative composition"** comprising danazole which differs from the formulation taught by Ragavan1; and the exhibit 2 illustrates that **"a topical, transvaginal**

formulation does not permeate the skin". The declaration, therefore, compares the composition comprising danazol in **a transvaginal formulation** not the formulation taught by Ragavan1. Moreover, the "quantitative composition" does not comprise **alcohol** which is a carrier taught by Ragavan1. Thus, it does not appear that Applicants have compared the claimed composition and with that of the closest prior art (Ravagan1). Applicants are reminded that when relying on comparative testing, the applicant is under a duty to compare his claimed invention with the closest prior art (i.e. Ravagan1) See, In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979); In re Merchant, 575 F.2d 865, 197 USPQ 785 (CCPA 1978); Ex parte Beck, 9 USPQ 2d 2000, 2002 (Bd. Pat. App. & Int. 1987) ("comparative evidence, to be effective, must compare the claimed subject matter with the closest prior art"); Ex parte Meyer, 6 USPQ2d 1966, 1968 (Bd. Pat. App. & Int. 1988) ("An applicant relying upon a comparative showing to rebut a prima facie case of obviousness must compare his claimed invention with the closet prior art.").

Further, Applicants' data comprising hydro-alcoholic gel #1 and hydro-alcoholic gel #2 have been carefully considered. Applicants are referring to the unexpected finding on Exhibit 5, page 5, table 2, that 15% pyrrolidone in the presence of 47% alcohol enhanced the danazol flux rate of hydroalcoholic gel#2 which has a rate of flux twice that seen with oleyl alcohol alone. However, this is not found to be persuasive because the data is not commensurate in scope of disclosures in the specification. The employment of "dehydrated alcohol" in the gel #1 and the gel #2 is not commensurate of what is disclosed in the specification. The instant specification employs for example,

oleyl alcohol. (see page 12). However, there is no disclosure of Applicants' demonstrate examples comprising the employment of "dehydrated alcohol" in the declaration. Therefore, the data in the declaration is not commensurate in scope of disclosure in the specification.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
September 17, 2009